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Prostate cancer brachytherapy

Urethral stricture following high dose rate brachytherapy for prostate cancer

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ABSTRACT

Purpose: To evaluate the incidence, timing, nature and outcome of urethral strictures following high dose rate brachytherapy (HDRB) for prostate carcinoma.

Methods and materials: Data from 474 patients with clinically localised prostate cancer treated with HDRB were analysed. Ninety percent received HDRB as a boost to external beam radiotherapy (HDRBB) and the remainder as monotherapy (HDRBM). Urethral strictures were graded according to the Common Terminology Criteria for Adverse Events v3.0.

Results: At a median follow-up of 41 months, 38 patients (8%) were diagnosed with a urethral stricture (6-year actuarial risk 12%). Stricture location was bulbo-membranous (BM) urethra in 92.1%. The overall actuarial rate of grade 2 or more BM urethral stricture was estimated at 10.8% (95% CI 7.0–14.9%), with a median time to diagnosis of 22 months (range 10–68 months). All strictures were initially managed with either dilatation ($n = 15$) or optical urethrotomy ($n = 20$). Second line therapy was required in 17 cases (49%), third line in three cases (9%) and 1 patient open urethroplasty (grade 3 toxicity). Predictive factors on multivariate analysis were prior trans-urethral resection of prostate (hazard ratio (HR) 2.81, 95% CI 1.15–6.85, $p = 0.023$); hypertension (HR 2.83, 95% CI 1.37–5.85, $p = 0.005$); and dose per fraction used in HDR (HR for 1 Gy increase per fraction 1.33, 95% CI 1.08–1.64, $p = 0.008$).

Conclusions: BM urethral strictures are the most common late grade 2 or more urinary toxicity following HDR brachytherapy for prostate cancer. Most are manageable with minimally invasive procedures. Both clinical and dosimetric factors appear to influence the risk of stricture formation.

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Reports of escalation of radiation dose for the curative treatment of localised prostate cancer have increasingly demonstrated improvements in cancer control compared to the standard doses [1–3]. Many of the reports relate to external beam techniques using three-dimensional conformal radiotherapy (3D-CRT) [1,2] or intensity-modulated radiotherapy (IMRT) [3] to limit dose to normal tissues so that tolerances are not exceeded. An alternative approach is to use temporary high dose rate brachytherapy (HDRB), typically in conjunction with moderate dose external beam radiotherapy [4–6]. The physical properties of HDRB result in rapid dose fall-off, such that steep dose gradients can be theoretically achieved to protect the immediately adjacent normal tissues, such as the rectum. Technically, the desired dose can be tightly conformed to the target volume with HDRB, reducing the amount of tissue that has to be treated compared with external beam therapy. Biologically, there is also evidence that many prostate cancers may be particularly sensitive to large radiation fraction sizes, which HDRB lends itself to well [7,8]. Theoretically, doses which may be biologically equivalent to 90 Gy or more can be delivered without the need for a prolonged course of treatment.

HDRB has, to date, been reported as having low rates of bowel and urinary morbidity [5,6,12], with our prospective dose-escalation study [9] experience paralleling these studies. Apparent in these data was, however, an apparent trend for the evolution of grade 2 or greater urinary toxicity over a number of years. It is known that HDRB can be complicated by a significant incidence of post-treatment urethral strictures; an outcome not specifically captured at the time of our initial phase II study. This study, therefore, specifically evaluates the clinical features of urethral stricture as a complication within a more substantial HDRB experience at the Peter MacCallum Cancer Centre (PMCC) since the inception of the program in 1997.

Methods

In total, data for 474 patients with clinically localised prostate cancer treated between September 1997 and September 2005 were available for analysis. All were required to have histologically proven adenocarcinoma of the prostate with a clinical stage of T1-3N0M0, as defined by staging investigations at the clinician's discretion. The initial 108 HDRB boost patients were enrolled on

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a prospective Phase 1/2 dose-escalation protocol using HDRB in combination with external beam radiotherapy for men with localised or locally advanced disease. This protocol called for treatment with four fractions of either 4 or 5 Gy over 2 days, which was undertaken in all but three cases. Subsequently, the schedule was changed to three fractions over 2 days (which were most often 6.5 Gy each) as the program became established as a part of routine care. A further 47 patients have been part of an ongoing experimental program of high dose rate monotherapy. For patients not on a prospective protocol, the case records were reviewed retrospectively to assess the outcomes. If routine follow-up was not being performed at PMCC, the last medical practitioner to review the patient was directly contacted to obtain their status. Specific note was made of previous trans-urethral resection of the prostate (TURP), and the development of urinary obstruction, which was defined according to the Common Terminology Criteria for Adverse Events CTCAE v3.0 (Table 1). Two cases with a past history of urethral stricture were excluded leaving 472 cases for analysis. Both the prospective and retrospective studies received approval from our Human Research Ethics Committee.

High dose brachytherapy was given as a boost (HDRBB) to external beam radiotherapy in 425 patients, using methods outlined previously [10]. In brief, external beam radiotherapy was delivered using 18 MV photons via a 3- or 4-field technique to cover the prostate or the prostate plus the seminal vesicles (if clinical stage T3b). The HDRB cannulae were inserted by the trans-perineal approach into the prostate under ultrasound and image intensifier guidance, most often under spinal anaesthesia. Patients were inpatients for the duration of the brachytherapy. At the start of the program volume reconstruction was performed using orthogonal films in conjunction with ultrasound images, and subsequently with CT planning. HDR brachytherapy was delivered using an Iridium-192 stepping source (MicroSelectron™, Nucletron NV). Urethral doses (calculated at the centre of each urethral outline each 5 mm) were constrained to be $\leqslant$120% of prescribed dose. The techniques for needle position verification evolved as the program proceeded, from measurement of external catheter length initially to the current approach of fiducial seed placement and pre-treatment fluoroscopic imaging. For those receiving HDR as a boost, the EBRT component was given prior to the HDR in 94% of cases ($n = 401$), using a dose of 46 Gy in 23 fractions in most cases ($n = 414$), with the remainder having 45 Gy in 25 fractions ($n = 7$), 44 Gy in 22 fractions ($n = 3$), or 40 Gy in 20 fractions ($n = 1$). The HDR brachytherapy boost was given in a single implant as 19.5 Gy in three daily fractions typically ($n = 278$), with smaller numbers having 20 Gy in four fractions ($n = 90$), 16 Gy in four fractions ($n = 54$), 14 Gy in three fractions ($n = 2$) or 10 Gy in a single fraction ($n = 1$). HDR brachytherapy as monotherapy (HDRBM) was given in three fractions over 3 days using a single implant at one of the three dose levels; 30 Gy ($n = 18$), 31.5 Gy ($n = 20$), or 33 Gy ($n = 9$). A nominal equivalent dose in 2 Gy fractions was calculated using an α/β ratio = 3 Gy ($2GyNED_3$) using a linear–quadratic relationship as follows: $2GyNED_3$ = total dose$^{\times}$ ((3 + dose per fraction)/5), summed for each phase if both EBRT and HDR given.

Table 1
CTCAE v3.0 criteria for urinary obstruction.

Grade	Urinary obstruction	Urinary incontinence
1	Asymptomatic, radiographic or endoscopic findings only	Occasional (e.g., with coughing, sneezing, etc.), pads not indicated
2	Symptomatic but no hydronephrosis, sepsis or renal dysfunction; dilation or endoscopic repair or stent placement indicated	Spontaneous, pads indicated
3	Symptomatic and altered organ function (e.g., sepsis or hydronephrosis, or renal dysfunction); operative intervention indicated	Interfering with ADL; intervention indicated (e.g., clamp, collagen injections)
4	Life-threatening consequences; organ failure or operative intervention requiring complete organ resection indicated	Operative intervention indicated (e.g., cystectomy or permanent urinary diversion)
5	Death	–

In total, 41% of cases (188 HDRBB and 7 HDRBM cases) were treated with androgen deprivation (AD) in addition to radiotherapy. In all but three cases, this was commenced prior to radiotherapy. The median duration of this neoadjuvant therapy was 6 months (IQR 5.5–7 months), and in 30 cases this was continued post-radiotherapy for a median duration of 16 months. Biochemical failure was defined as a rise by 2 ng/mL or more above the nadir PSA as per the Phoenix definition [11], with follow-up commencing on the last day of radiotherapy.

Statistical methods

Differences between proportions and continuous variables were calculated using χ^2 and *t*-tests, respectively. Actuarial rates of urinary obstruction were calculated using Kaplan–Meier methods, with confidence intervals obtained using bootstrap re-sampling ($n = 500$) from within the Hmisc and Design libraries of the *R* statistical language. Cox proportional hazards modelling was used for multivariate statistics. Statistics were always calculated two sided, and significance attained at the $p \leqslant 0.05$ level.

Results

The patient and tumour demographics are shown in Table 2. HDRBB cases had significantly more advanced tumours than the monotherapy patients on the basis of stage ($p < 0.001$) and PSA ($p < 0.001$), while the GS distribution was not significantly different. The known rates of co-morbid conditions of interest were not significantly different between the treatment types. The HDRBM group had significantly shorter follow-up than the HDRBB group ($p < 0.001$). At the time of analysis 29 patients had died; 6 of prostate cancer. Biochemical failure had occurred in 106 men, with an actuarial 5-year freedom from biochemical failure of 68.7% (95% confidence interval (CI): 63.4–73.9%).

The indwelling catheter (IDC) was removed on the 1st post-implant day (PID) in 79% ($n = 372$), and within the 1st week in a further 19% ($n = 86$). Seven cases had the IDC removed between 1 week and 1 month, and six between 1 and 13 months. One case remained catheter dependant at 3.8 years following chronic retention and multiple endoscopic prostatic resection procedures.

Late urinary toxicity

At the time of analysis, 38 patients (8%) had been diagnosed with grade 2 or more urinary tract obstruction. The estimated grade 2 or more obstruction rate for the total cohort at 6 years was 12.0% (95% CI 8.3–16.2%). For the subgroup of HDRBB, the rate was 11.2% (95% CI 7.5–15.5%) at 6 years, and for HDRBM the rate was 15.3% (95% CI 2.8–32.1%) at 3 years. The diagnosis and location of the obstructive lesion were confirmed by urethroscopy in all but the single case, which was diagnosed on the basis of symptoms and the passage of sounds. The obstructing lesion was located at bladder neck ($n = 2$; 0.4%); prostatic urethra ($n = 1$; 0.2%); and bulbomembranous urethra ($n = 35$; 7.4%).